Exhibit A

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624 617-951-7000 F 617-951-7050
BOSTON NEW YORK PALO ALTO SAN FRANCISCO WASHINGTON, DC www.ropesgray.com

October 11, 2006

Adam Wright
(617) 951-7956
adam.wright@ropesgray.com

BY HAND DELIVERY

Thomas M. Sobol, Esq.
Hagens Berman Sobol Shapiro LLP
One Main Street
Cambridge, MA 02210

Re: *In re Pharmaceutical Industry Average Wholesale Price Litigation*, MDL 1456

Dear Mr. Sobol:

Pursuant to Schering-Plough Corporation's Response to the Court's Order on Plaintiffs' Emergency Motion to Compel the Production of Documents and Data Underlying Criminal Plea and Settlement Agreement, filed today, enclosed please find the documents referenced therein. These documents have been Bates labeled SPW0042588 to SPW004271, and are produced pursuant to the protective order in effect in this action.

Very truly yours,

Adam Wright

Enclosures

cc: Steve Berman, Esq. (w/ enclosures via Federal Express)

THE ROLE OF INTERFERON ALFA IN SUPERFICIAL BLADDER CARCINOMA

Schering® ONCOLOGY BIOTECH

FACULTY PLANNING MEETING

SEPTEMBER 28, 2001

KENILWORTH, NEW JERSEY

Marucci, Maria

From: Mrsnwilson@aol.com
Sent: Thursday, December 06, 2001 3:01 PM
To: marylee.decosimo@spcorp.com; maria.marucci@spcorp.com; mingram@projectsinknowledge.com; ppeterson@projectsinknowledge.com
Subject: Bladder Cancer Ad Board final

Just confirmed the last bladder cancer meeting as follows:

2/23 - Pennsylvania
Faculty: Robertson/Eastham
Venue: Nemacolin Woodlands Resort
Holding space. Please call to confirm and set-up asap.
Contact Andy Idzik, phone 724-329-6383

Any questions, please call. Regards, Nancy

Nancy Wilson, Sr. Project Director
Projects In Knowledge, Inc.
One Harmon Plaza Tel. (201) 617-9700x137
Sixth Floor Fax (201) 617-5606
Secaucus, New Jersey 07094

Marucci, Maria

From: Mrsnwilson@aol.com
Sent: Thursday, December 06, 2001 10:42 AM
To: marylee.decosimo@spcorp.com; maria.marucci@spcorp.com
Cc: mingram@projectsinknowledge.com; ppeterson@projectsinknowledge.com
Subject: Update Bladder Cancer Ad Boards

Dear Marylee and Maria --

Two dates nailed down -- and the last one looks promising.

January 26 - Pasadena, CA
Faculty: Choudhury/Sawczuk
Venue: Huntington Hotel & Spa (R/C)
(this is DM's first choice hotel - we will have to do classroom or rounds)
Holding space, please call today to confirm and set-up.
Contact Jill Hilts, phone 626-585-6408

February 9 - Ft. Lauderdale FL
Faculty: Robertson/Eastham
Venue: Marriott Harbour Beach
Holding space, please call today to confirm and set-up
Contact Pat Bunin, phone 954-766-6172

Pending: 2/23 - Pennsylvania
Faculty: Robertson/
Venue: Nemacolin Woodlands Resort
Holding space. Waiting on 2nd presentor
Contact Andy Idzik, phone 724-329-6383

Any questions, please call. Regards, Nancy

Nancy Wilson, Sr. Project Director
Projects In Knowledge, Inc.
One Harmon Plaza Tel. (201) 617-9700x137
Sixth Floor Fax (201) 617-5606
Secaucus, New Jersey 07094

1548 BLADDER CANCER ADVISORY BOARD SERIES – DELIVERABLES

- **Bladder Cancer Advisory Board Series Faculty Planning Meeting**

NJ/NY site for 1-day meeting for the development of content
8 faculty attendees, including Chair
Development of slide kit with lecture notes

- **Bladder Cancer Advisory Board Series Overview**

6 Advisory Board Meetings in series
20 attendees maximum
2 faculty plus 1 Schering faculty
Beginning Fall 2001
9:00 am - 2:00 pm with working lunch (timing is flexible)
Attendee invitations distributed by field force and general mailing to local audience (sent by Fed Ex to reps and by Priority Mail to local audience)
Executive Summary

- **Projects In Knowledge Services and Responsibilities**

Initial contact with faculty
Faculty recruitment, management, and honoraria
Project management
Liaise with Schering in developing faculty, content, and meeting
Content development including editorial and graphic development of objectives, invitations, meeting materials, and slides
On-site management of all logistics (oversight of catering, AV, departures, content, faculty, and attendees)
Production of invitations and distribution to field force
Attendee database management and coordination with Schering
Development and execution of the Executive Summary (all meeting attendees/faculty to receive the 10-12 page Executive Summary)

- **Schering Responsibilities**

Attendee honoraria and expenses
District involvement (distribution of invitations, suggested sites/attendees/faculty)
Contract and fiduciary management of:
-hotel (meeting space, sleeping rooms, catering, local AV, local temp service)
-travel arrangements (attendee and PIK/Schering staff), including air and ground

Bladder Ca mtgs

Temodar™
temozolomide
capsules

Nancy Wilson / Lorraine 860-347-3121
Projects in Knowledge

11/17 NJ - Absecon Eastham, Cohen
mod - Tobin

by Fri - receive letter : 4 wks. to invite
email get info.

11/17 San Antonio Choudury DM:
Robertson Pfister

12/8 San Fran. Sawchuk M. Metheny
Robertson

---

3 left

So. Cal. - Saenz (3) possible Jan. 12 th
Penn. - Mark Mango (not 19) 26
Fl - Jepsen (not 12) → 19th

1548 Bladder Cancer Advisory Board Meeting Series

Faculty Contact Sheet ♦ 1548-FacultyContacts8-27.doc

SERIES CHAIR Leonard G. Gomella, MD Kimmel Cancer Center Thomas Jefferson University 1025 Walnut Street, 11th Floor Philadelphia, PA 19107 215-955-1702------Conchita 215-923-1884 fax Leonard.Gomella@mail.tju.edu Conchita.Ballard@mail.tju.edu WILL PHONE IN SEPT. 28 FROM OUT OF TOWN.	James A. Eastham, MD Memorial Sloan Kettering Cancer Center Department of Urology Box 27 – Room C-107 1275 York Avenue New York, NY 10021 212-639-2212 212-717-3175 fax eastham@mskcc.org SEPT. IS BOOKED. CAN'T COME. WILL DO ROLLOUTS	Donald L. Lamm, MD West Virginia University Medical Center Department of Urology R.C. Byrd Health Sciences Center – 5th Floor Morgantown, WV 26506 304-293-2706 304-293-2807 fax CAN'T CHAIR SERIES CAN'T MAKE SEPT MTG CALL FOR ROLLOUTS.	Cory N. Robertson, MD Duke University Medical Center Division of Urology Box 3bUMC 3707 Room M452 – Green Zone Duke South Durham, NC 27710 919-681-6758 ---- Susan 919-681-8074 fax 8/23/01 – CAN'T MAKE 9-28 WILL DO ROLLOUTS
Muhammad S. Choudhury, MD, FACS Chairman, Department of Urology New York Medical College Munger Pavilion Room 456 Valhalla, NY 10595 914-594-4300 914-594-4394 fax Muhammad_Choudhury@NYMC.edu CAN MAKE SEPTEMBER 28.	Thomas E. Keane, MB ChB Emory Clinic Section of Urology 1365 Clifton Road NE Atlanta, GA 30322 404-778-5951 404-778-4006 fax CAN MAKE SEPTEMBER 28.	William A. Larchian, MD Cleveland Clinic EMH Urological Institute Dept. of Urology 125 E. Broad St., Ste 208B Elyria, OH 44035 440-329-7315---- Terry 440-329-7316 fax larchiw@ccf.org CAN MAKE SEPTEMBER 28	Ihor Stefan Sawczuk, MD Hackensack University Medical Center 20 Prospect Ave, Suite 703 Hackensack, NJ 07601 201-336-8090 201-336-8220 fax Isawczuk@humed.com CAN MAKE SEPTEMBER 28.
Steven I. Cohen, MD Divisional Director, Urology Roger Williams Medical Center Urologic Surgeons of New England 125 Carliss Street Providence, RI 02904 401-274-6565 401-331-2370 fax sicppmd@earthlink.net CAN MAKE SEPTEMBER 28.	Erica A. Klein, MD The Cleveland Clinic Foundation Department of Urology 9500 Euclid Avenue, Desk A-100 Cleveland, OH 44195 216-444-5591 Linda CAN'T CHAIR SERIES	Michael A. O'Donnell, MD University of Iowa Department of Urology 200 Hawkins Drive – RCP Iowa City, IA 52242 319-384-6040 319-384-6043 fax Pat CAN'T CHAIR SERIES	

Maria M —
Please put w/
Bladder Ad Board
file. This invoice
goes against $75,000
put aside for logistics.
Tx
MM

hotel nikko san francisco
222 Mason Street, San Francisco, CA 94102
Telephone 415-394-1111

SCHERING PLOUGH BLADDER CORP
ATTN: MS. MARYLEE DECOSIMO
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-053

JANUARY 04, 2002

ACCT# CWTM

******INVOICE******

Please indicate invoice account number as it appears on this statement on back of check and enclose this portion with your payment to ensure proper credit to your account.

Date	Reference	Charges	Credits	Balance Due
01/04/02	SCHERING PLOUGH CORP FRM 12/04/01 TO 12/11/01	$ 7,643.87*		

0330-37710-3610-9893-1008121
1/21/01

81

TM

MOUNT

600.00-
600.00-
28.57
28.57
27.00
365.61
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27.00
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27.00
27.00
270.75
270.75

Current	30 To 60 Days	60 To 90 Days	Over 90 Days	Total Due

Statements due when rendered. Monthly service charge of 1½% will be added to past due accounts over 30 days.
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12/06/01 XFR FRM	GROUP SETTLEMENT KIRKDOFFER CHARLE 1807 FRM 12/07/01 TO 12/08/01	372071856848	
12/08/01 XFR FRM	GROUP SETTLEMENT KILLIAN STEVE 1201 FRM 12/07/01 TO 12/08/01	372291971023	

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FOLIO HNSF 5-23-0

11/17/01

Temodar™
temozolomide
capsules

Bladder Ad Board

Valstar - 90% pts. experience s/e
6-8% RR long-term (2 yrs.)
- 1 yr. 18%
- 2 yrs. all pts. got cystectomy

original study

Eastham withdrew from study s/c of poor RR + s/e

IFN + BCG for naive pts. → pts. w/ intermed. + high grade tumors need to justify cost of IFN

NJ mtg → 28p.
very interactive thru-out

Eastham - CTC very positive
Cohen agreed

Cohen - good ck. of cost issue →
comparison of cnc. therapies
& their cost (cycles, etc.)
- not much concern about cost

Please see accompanying full Prescribing Information.

Districts can invite max of 25 MDs. We are covering Honorarium (₹500) & expenses (travel) for MDs.

SCHERING ONCOLOGY/BIOTECH
2000 GALLOPING HILL RD.
KENILWORTH, NEW JERSEY 07033

FAX NO. (908) 298-7500

TO:

Patty Peterson

COMPANY:
Projects in Knowledge

FAX #:
201-617-5606

TOTAL # OF PAGES:
4 (including cover)

FROM:

- ☐ PATRICIA BUSH (908) 298-4623
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  FAX (609) 448-1530
- ☐ BEVERLY CASARICO (908) 665-8090
  FAX (908) 665-4086
- ☐ West Coast PCC Manager Vacant
  FAX
- ☐ DEBORAH MEAD (908) 298-4557
  MARIA MARUCCI 908-298-2239
- ☒ MARY NAUGHTON (908) 298-2465

MESSAGE: Regarding Cardiac Tox. . .
There have been a V. small number (3) of cardiac Adverse Events reported for pts. on the O'Donnell protocol (BCG + IFN). They were deemed "unrelated" to therapy. However the protocol was amended ... see wording on final page. All 3 pts reported on protocol amendment had history of cardiac disease.

QUICK FAX OfficeMax

To: Mary Naughton	From: Alice Senko
Co./Dept.	Co./Dept.
Fax: (908) 298-7500	Fax:
Phone#	Phone: (416) 657-6012
Note:	E-mail:

Protocol Amendment No. 4
Serious Adverse Event Update and Changes to Protocol Exclusion Criteria and Consent

As of 11/9/99, 165 new patients have been enrolled into the BCG plus Interferon-alpha National clinical trial from about 70 active sites throughout the US, many of which are running under the auspices of local IRBs or two National IRBs, Ethical Review Committee (ERC) or Western IRB (WIRB). Five reports of serious adverse events have been received during this period of time, 4 of which were felt by the site investigators to be UNRELATED to the study protocol and one of which was felt to be DEFINITELY RELATED. A specific chronological listing of these events with clinical summaries is listed below. Full details and primary data sheets are available upon request.

1. ***SAE:*** Dilated Renal Pelvis (Unilateral Right Hydronephrosis). ***Patient ID:*** ***Onset Date:*** 7/23/99. ***Resolution Date:*** 8/13/99. ***Intensity:*** Moderate. ***Action Required:*** Endoscopic surgery for stent placement X 2; temporary interruption of study drugs. ***Relationship to Study Drug:*** UNRELATED. ***Description:*** After receiving 2nd study drug treatment of 1/3 dose BCG plus 50 MU Interferon-alpha, asymptomatic patient noted to have elevated BUN - 90, creatinine - 5.7 and hydronephrosis on ultrasound. Cystoscopic evaluation on 7/27/99 revealed right uretero-vesical junction stricture thought to be an unrecognized pre-existing condition from prior surgical removal of tumor near this site, and thus unrelated to study drugs. Stent placed. Treatment #3 held on 7/30/99 due to hematuria resulting from stenting procedure. Repeat ultrasound and KUB showed migration of stent and continued hydronephrosis. Stent replaced 8/2/99. Treatment held 8/6/99 for hematuria. On 8/13/99 BUN - 48; Creatinine 2.2. Patient completed remainder of 4 treatments without further events and on first evaluation 10/26/99 has no residual cancer. ***National Office Action:*** None required.

2. ***SAE:*** Sick Sinus Syndrome; palpitations and dizziness without loss of consciousness. ***Patient ID:*** lpt- ***Onset Date:*** 9/01/99. ***Resolution Date:*** 9/03/99. ***Intensity:*** Moderate. ***Action Required:*** Hospitalization and placement of cardiac pacemaker; temporary interruption of study drugs. ***Relationship to Study Drugs:*** UNRELATED. ***Description:*** Two days after first uneventful induction treatment with 1/3 dose BCG plus 50 MU of Interferon-alpha patient reported palpitations to her cardiologist. Had mild fever <100.5 F from prior procedure < 24 hour duration along with mild flu-like symptoms and arthralgias. Known prior history of sick sinus syndrome, paroxysmal atrial fibrillation, right carotid endarterectomy, aortobifemoral bypass, multiple lacunar infarcts, ischemic heart disease without history of MI, iatrogenic hypothyroidism, and idiopathic hypertension. Current meds: Betapace, Hyzaar, Micro-K, Norvasc, Synthroid, and Mevacor. Admitted to hospital 9/2/99 for near-syncope. Cardiac pacemaker placed 9/3/99 and discharged home 9/5/99. Scheduled study drug treatment #2 was held due to recentness of procedure and resumed following week. Patient completed remainder of therapy without further events. ***National Office Action:*** No immediate action required (but see later recommendations).

3. ***SAE:*** Prolonged fever; presumed BCG infection. ***Patient ID:*** ***Onset Date:*** 9/17/99. ***Resolution Date:*** 9/25/99. ***Intensity:*** Moderate. ***Action Required:*** Study termination and institution of 12 weeks of antituberculosis medication (INH, rifampin, Vitamin B6).

 REDACTED

Relationship to Study Drug: DEFINITELY RELATED. ***Description:*** After receiving 1st study drug treatment with full dose BCG + Interferon-alpha (no trauma reported), patient noted to become febrile to 102. Intermittently remained febrile throughout week along with severe dysuria and urgency. Urine culture: no growth. Bladder scan revealed 183 post-void residual. Treatment with INH, rifampin and Vitamin B6 started 9/24/99. Urinary symptoms resolved at this time. Remained afebrile after 9/25/99. ***National Office Action:*** Agreed with site investigator that study termination and 12 weeks of anti-TB medication was appropriate. Given this is a known adverse event associated with intravesical BCG use with a reported incidence of ~5% in BCG monotherapy studies, and is specifically mentioned in the consent form, no alterations in protocol have been recommended.

4. ***SAE:*** Congestive heart failure. ***Patient ID:*** 1pt. ***Onset Date:*** 9/28/99. ***Resolution Date:*** 9/29/99. ***Intensity:*** Moderate. ***Action Required:*** Hospitalization and diuretic use; temporary interruption of study drugs. ***Relationship to Study Drug:*** UNRELATED. ***Description:*** Patient noted to have shortness of breath on 9/28/99 after receiving 5th dose of 1/3 BCG plus 50 MU Interferon-alpha. No associated trauma, fever, or chills. Mild dysuria and frequency. No chest pain, pedal edema, mental status changes, cough or sputum production. Past medical history positive for coronary disease, congestive heart failure, hypertension, NIDDM, and arthritis. Physical exam notable for basilar rales. PO2 - 94% on room air. Chest X-ray consistent with congestive heart failure. Patient responded promptly to lasix diuresis. Received 6th (final) treatment after additional one week delay without adverse event. ***National Office Action:*** No immediate action required (but see later recommendations).

5. ***SAE:*** Angina. ***Patient ID:*** ***Onset Date:*** 11/08/99. ***Resolution Date:*** evaluation in progress. ***Intensity:*** Moderate. ***Action Required:*** Cardiac evaluation by primary care physician; temporary interruption of study drugs. ***Relationship to Study Drug:*** UNRELATED. ***Description:*** Patient noted to be complaining of 2 weeks of intermittent angina requiring increased use of nitro patches first brought up during 5th treatment evaluation. Was receiving full dose BCG plus 50 MU Interferon-alpha. Had mild (grade 1) flu-like symptoms < 24 hours but no fever. Received 5th treatment with no adverse events. Past medical history notable for coronary artery disease with 4-vessel coronary bypass grafting in 1988 and angioplasty (3 vessels) in 1996. History of stroke post-op from CABG with residual left sided weakness and known angina on exertion. Pre-treatment meds included nitropatch, lasix, norvasc, atenolol, levcor, and prevacid. ***National Office Action:*** Recommended holding further treatment until cardiac evaluation by primary care. (see also other recommendations below).

While all three cardiac-related SAEs are listed by the site investigators as unrelated to the study drugs, with this most recent report from 11/9/99 the issue of potential cardiotoxicity deserved specific attention. Examining records of over 70 patients treated at the Beth Israel Deaconess Medical Center with BCG or combination BCG plus interferon over the past 4 years, 2 other cardiac-related SAEs also felt to be unrelated to these drugs were found. One case bore similarity to #2 above where a patient with a known internal ventricular fibrillator had intermittent syncope and defibrillator firing requiring hospitalization during the time of active BCG monotherapy treatment. His cardiologists felt this was unrelated to the treatment and he also was able to resume therapy. Another case was similar to #4 above in which a patient with history of significant underlying CHF required hospitalization a few days after receiving combination therapy full dose BCG plus 50MU Interferon. Low-grade fever and chills were noted. Ultimately

REDACTED

found to have pseudomonas pneumonia on top of CHF. Treatment was interrupted for 3 months then resumed at 1/10th BCG plus 50 MU Interferon. Five days after 2nd re-treatment again hospitalized for CHF. No preceding fever or chills noted; only mild dysuria. No further treatments given. In none of the cases then and now were there high fevers or rigors directly associated with the events although most patients experienced mild versions of these at some point during therapy.

Intravesical interferon-alpha has been reported to cause a transient flu-like illness with fevers and chills in as much as 20% of cases yet no direct cardiac toxicity. A previous review of over 2600 patients receiving intravesical BCG monotherapy (Lamm, 1989) noted only that there were some cardiac events also not thought directly related to BCG. Yet, the authors felt that the temporary flu-like illness often seen within the first 48 hours after treatment can place additional physiological stresses on a compromised cardiovascular system. Patients with bladder cancer are often elderly current or ex-smokers with a high underlying prevalence of cardiac disease. The National Study Data Safety Monitoring Committee consisting of 4 physicians familiar with biological therapy including high dose systemic interleukin and interferon therapy concurs that there is at least some room for concern. Accordingly, the protocol and consent forms are to be amended as follows:

PROTOCOL AMENDMENT:

Exclusion Condition: Patients with poorly-controlled, active cardiac disease including congestive heart failure, serious arrhythmia, and ischemia are excluded from study entry. Patients with a history of medically-controlled, stable cardiac disease should undergo an appropriate cardiac evaluation by their medical doctor to determine if they are at serious risk for cardiac disease exacerbation under circumstances during which they may be physiologically stressed by fevers and chills known to accompany BCG and/or Interferon-alpha therapy. Caution should be exercised in treating such patients, weighing cancer risk against possible treatment toxicity.

CONSENT AMENDMENT: (to be added under Potential Risks)

No direct heart-related side-effects have been reported with either BCG or interferon-alpha when given in the bladder, however, both agents are known to occasionally cause transient fevers and chills that can place extra stresses on the heart. Although no clear evidence of exaggerated fevers or chills has been observed in previous reported studies of combination therapy, there is at least some theoretical potential that such side effects may be either more frequent, more intense, or both. Some patients with known pre-existing serious heart diseases including angina, congestive heart failure, and serious rhythm disturbances have experienced temporary worsening of these conditions during the active treatment period with combination BCG plus Interferon-alpha. Although a direct cause and effect relationship has not been determined in any of these cases, caution dictates that patients with severe underlying heart disease not adequately controlled by medication not be treated with this therapy. Those with less severe conditions adequately controlled with medication should first consult their primary care physicians or cardiologists to determine if they are at any significantly increased risk due to the possible increased stresses that may accompany this treatment.

10/26/01 13:01 FAX 908 298 7500 SCHERING LABS ONC/BIO ☑001

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0922
CONNECTION TEL	912016175606
SUBADDRESS	
CONNECTION ID	
ST. TIME	10/26 13:00
USAGE T	01'02
PGS. SENT	4
RESULT	OK

SCHERING ONCOLOGY/BIOTECH
2000 GALLOPING HILL RD.
KENILWORTH, NEW JERSEY 07033

FAX NO. (908) 298-7500

TO: Patty Peterson

COMPANY: Projects in Knowledge

FAX #: 201-617-5606

TOTAL # OF PAGES: 4 (including cover)

FROM:

- ☐ PATRICIA BUSH (908) 298-4623
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  FAX
- ☐ DEBORAH MEAD (908) 298-4557
- MARIA MARUCCI 908-298-2239
- ☒ MARY NAUGHTON (908) 298-2465

MESSAGE: Regarding Cardiac Tox. ... (3) of Cardiac Adverse

Marucci, Maria

From: Naughton, Mary
Sent: Thursday, October 18, 2001 1:53 PM
To: Marucci, Maria
Subject: FW: Bladder Cancer update

---Original Message---
From: Patty Peterson [mailto:ppeterson@projectsinknowledge.com]
Sent: Thursday, October 18, 2001 11:25 AM
To: Mary Naughton; Val Taccogna; Marylee DeCosimo
Subject: Bladder Cancer update

Hi Mary:

Molly Metheny is pleased with Ihor Sawczuk (Hackensack) and Cory Robertson (Duke) and wants to proceed with Dec 8 schedule. So that meeting is now confirmed.
Invitations will be worked on next week, and will be forwarded to reps in that area beginning Monday 10/29.

Thanks, patty

Projects In Knowledge, Inc.
One Harmon Plaza Tel. (201) 617-9700
Sixth Floor Fax (201) 617-5606
Secaucus, New Jersey 07094

---------- End Forwarded Message ----------

Patty Peterson
Projects In Knowledge, Inc.
One Harmon Plaza
Secaucus, NJ 07094
voice: 201 617 9700 Ext 123
fax: 201 617 5606

Naughton, Mary

From: Mead, Debbie
Sent: Tuesday, September 25, 2001 11:05 AM
To: Naughton, Mary
Subject: FW: Bladder Cancer Faculty Planning Meeting 9-28

We should discuss and have a plan. You, Jorge, me?. I think Val may be traveling.

—Original Message—
From: Beth Monica [mailto:bmonica@projectsinknowledge.com]
Sent: Tuesday, September 25, 2001 10:56 AM
To: MEAD, DEBBIE
Cc: Michele Ingram
Subject: Bladder Cancer Faculty Planning Meeting 9-28

Dear Debbie:

Hope you're well. I will be onsite on Friday for the Faculty Planning Meeting in K-1-2A. Can you tell me what the procedure is for the faculty and PIK people to check in upon their arrival at Schering (Schering contact name, etc.)?

Those who will be in attendance are:

Dr. Thomas Keane
Dr. William Larchian
Dr. Muhammad Choudhury
Dr. Steven Cohen
Dr. Ihor Sawczuk
Patty Peterson or Michele Ingram (PIK)
Beth Monica (PIK)
Lauren Cerruto (PIK)

Gomella – on phone

I just want to send the doctors a final confirmation about what to do and where to go once they arrive.

I also wanted to confirm that a speakerphone will be available and need to find out what the dial-in number is for Dr. Leonard Gomella (program chair). He is going to be out of state, but will be calling in for the meeting.

Thanks, Debbie.

Regards,

Beth

Beth Monica
Senior Project Director/
Director of Education
Projects In Knowledge, Inc.
One Harmon Plaza, 6th Floor

ph 201-617-9700 x114
f 201-617-5606
bmonica@projectsinknowledge.com

Naughton, Mary

From: Michele Ingram [mingram@projectsinknowledge.com]
Sent: Friday, October 05, 2001 11:39 AM
To: Mary Naughton
Cc: Patty Peterson
Subject: DM Update on Bladder Cancer Slide Kit and Advisory Board Meeting (1548)


DMUpdate3.doc

Dear Mary,

Attached is a note to the DMs regarding the status of the bladder cancer slide kit and advisory board meeting series. We drafted the note as though it comes from you, so please feel free to change it as you like before you send it. Or, if you would rather the message comes from us, just let me know and we will send it out from PIK.

The DMs slotted to have advisory board meetings are: Harry Durr, Tom Saenz, Molly Metheny, Sheri Jepsen, Mark Manzo, and Jeff Pfister.

Thanks, Mary, and have a great weekend.
-Michele

Michele Fallon Ingram
Asst. Vice President
Projects In Knowledge, Inc.
One Harmon Plaza
Secaucus, NJ 07094
(p) 201-617-9700, ext. 125
(f) 201-617-5606
(e) mingram@projectsinknowledge.com

Dear DMs:

On September 28, 2001, a faculty planning meeting was held at Schering for the development of content for the upcoming Advisory Board Meeting Series, Superficial Bladder Carcinoma. The planning meeting and series are chaired by Dr. Leonard G. Gomella of Kimmel Cancer Center/Thomas Jefferson University.

The faculty in attendance met to develop the content of what they believe will be "THE ULTIMATE SLIDE KIT ON SUPERFICIAL BLADDER CANCER." Their work at the meeting will allow Projects In Knowledge (responsible for content/project administration) to refine and produce a speaker slide kit and ancillary teaching cases for the series.

The series (6 regional, 4-hour meetings) is being developed to provide urologists with practical information on the use of Intron A + BCG in combination for the treatment of superficial bladder cancer, and to gather their perspectives on care, based on their direct clinical experience.

Projects In Knowledge, in conjunction with Schering, is in the process of scheduling dates, venues, and faculty presenters for each of the 6 meetings. These will be held on either11/17, 12/1 or 12/8. Each meeting will feature two faculty presenters, with a local urologist acting as host and encouraging interaction and discussion between the audience and faculty.

These meetings are being planned for Saturdays, from 10:00 AM to 2:00 PM, with continental breakfast and a working luncheon being provided. You will hear from Projects In Knowledge very soon regarding confirmations of dates, locations, and speakers. An honorarium of $500 will be provided to each physician attending for their participation in the meeting. Expenses for mileage and parking will be reimbursed.

Our target is 20 urologists in attendance at each meeting. In order to achieve this goal, we are asking DMs to encourage area reps to actively recruit for this meeting. Invitations will be sent to DMs prior to the meeting. For additional support, Invitations will also be mailed to urologists within a 20-30 mile radius of the meeting site. All participants must pre-register for this meeting.

No

12

call Nancy to check

Following completion of the series, Projects In Knowledge will prepare an Executive Summary of the proceedings, to be distributed to all urologists who attended the meetings.

We're very excited about this project and look forward to a successful series.

Lorraine

Naughton, Mary

From: Nancy Wilson [nwilson@projectsinknowledge.com]
Sent: Monday, October 15, 2001 12:16 PM
To: Mary Naughton
Subject: Bladder Cancer Ad Board Series

1548DraftInvitcNW10-10.doc

Dear Mary,

Attached is a copy of the invitation for the NJ meeting on November 17. This was very closely modeled after a similar sample invitation Val provided. Good news this morning from Cary Robertson MD from Duke U. He is available all three dates. Am waiting now to hear if he is willing to travel to west coast on 11/17. If so, we are free to book that meeting as well, with him presenting with Dr. Choudhury. This also opens up the possibility of holding a meeting on Dec 8 with Robertson and Dr. Sawczuk presenting. Will update you at day's end as to where we are at with all of this.

Meanwhile, please OK this letter, or return to me with your suggestions and I will revise. Also please check that I've gotten your title correct. Thanks Mary. Regards, Nancy Wilson

Nancy Wilson, Senior Project Director
Projects In Knowledge, Inc.
One Harmon Plaza Tel. (201) 617-9700x137
Sixth Floor Fax (201) 617-5606
Secaucus, New Jersey 07094

October 18, 2001

Dr. XXXXXX
XXXXXXX
XXXXX, XX XXXXX

Dear Dr. XXXXXX,

Schering Oncology Biotech is pleased to invite ~~your participation~~ you to participate in an Advisory Board Meeting entitled ***Superficial Bladder Carcinoma.*** This meeting is being held at the Seaview Marriott Resort in Absecon, New Jersey on Saturday, November 17, 2001 from 10:00 AM to 2:00 PM. The goals of this meeting are to share a broad base of clinical information on superficial bladder carcinoma, discuss the use of interferon alfa and BCG, and understand the needs of the oncology community in diagnosing and treating bladder cancer.

Meeting Registration: At your earliest convenience, please fax the enclosed ***Meeting Response Form*** to 201-617-5606 to confirm your attendance by November 7. Reservations received after this date cannot be guaranteed.

Faculty:

Steven I. Cohen
Divisional Director, Urology
Roger Williams Medical Center
Providence, Rhode Island

James A. Eastham
Memorial Sloan Kettering Cancer Center
New York, New York

Meeting Topics: These meetings will provide an overview of the epidemiology, natural history, diagnosis, staging, and management of superficial bladder carcinoma. The focus will be on recent data pertaining to intravesical therapies, particularly interferon and BCG, in the treatment of superficial bladder cancer. You will have an opportunity to provide your feedback regarding these data.

Honorarium: We are pleased to provide you with an honorarium of $500 for your active participation in the meeting.

Meeting Expenses: Schering Oncology Biotech will reimburse auto mileage expense for the meeting date. All food functions during the meeting are complimentary.

For meeting-related questions, please contact Nancy Wilson, Sr. Project Director at 800-772-8277, X154, or e-mail at bldrcancer@projectsinknowledge.com. For logistics questions please contact Marylee DeCosmo at 908-995-5664.

DELETE My Name & Sign Off I just spoke to Jorge, who said my name should not be on this.

THE CLEVELAND CLINIC FOUNDATION
Urological Institute

William A. Larchian, M.D.
Elyria Office
Office: 440/329-7315
Fax: 440/326-5487

seeking your consultation. Eighteen months prior to this visit, she experienced intermittent, painless, gross hematuria. She sought attention from her PCP who ordered an UA (>500 RBC's on HPF) and an IVP (negative).

She was referred to another urologist who obtained a C&S (no growth) and cytology (negative). He attempted an office cystoscopy which was unsuccessful due to a severe urethral stricture, calibrated at 8 Fr. She did not continue care with this physician.

Her symptoms have now returned and she has been referred to you.

Her medical history is significant for well controlled hypertension for the past 8 years. She has no urologic history other than stated above. She has never smoked cigarettes. She has never been pregnant. She has no surgical history.

On examination, her abdomen is soft, active bowel sounds and no CVAT. She does have LLQ tenderness to deep palpation. Her pelvic exam is unremarkable.

You repeat the above tests with similar results. You perform a urethral dilatation and cystoscopy under anesthesia. A 2.5 cm sessile lesion is noted in the trigone, just to the left of midline. You perform a TURBT of this lesion. A random bladder biopsy is also performed. Pathologic diagnosis of the lesion reveals TCCA, stage T1, Grade III, with no muscle invasion. The random biopsy is negative. A CT of the chest, abdomen and pelvis is unremarkable other than inflammation at the resected site.

You recommend:

1. Repeat cystoscopy in 3 months.
2. Restaging TUR ~~in 3 months~~.
3. A 6 week course of IVS BCG.
4. A 6 week course of combined IVS BCG/interferon. Do PS3
5. Radical cystectomy.

125 East Broad Street, #208, Elyria, Ohio 44035

REDACTED

The patient completes 6 weeks of BCG. Cytology is negative. Repeat TURBT reveals TCCA, stage T1, grade II, at the same site.

You recommend: (All reasonable)

1. Another 6 week course of BCG. (note: no study demonstrates this works).
2. Combination BCG/interferon. (1/3 dose)
3. Radical cystectomy.

~~4) restaging TUR at 6 weeks.~~

~~5) treat~~ Do P53

Following another 6 week course of BCG, she again has stage T1, grade III disease. Random biopsies are negative. A repeat CT of the chest, abdomen and pelvis is negative.

You recommend:

1. Another course of IVS BCG.

2. Combination BCG/interferon.

3. Radical cystectomy.

After a full discusion of benefits, risks and potential complications of all therapeutic options, she decides on combination therapy.

She receives 6 weeks of IVS, 1/3 dose BCG and 50 MU of Intron A. Restaging TUR is negative. She receives another 6 week course of the same. Restaging TUR is again negative. CT scans are negative.

She does not receive any further treatment. All cytologies are negative. Surveillance cystoscopies every 3 months for the first 2 years are negative. She continues with 6 month surveillance cystoscopies. She is now 3 years and 1 month since her last positive TCCA.

Educational Initiative in Urology

THE TREATMENT REPORTER UROLOGY

Release Date: April 30, 2001.
This newsletter has been planned, produced, and approved as a CME activity in accordance with the ACCME Essentials and Standards for Commercial Support. This ensuring activity will be reviewed within 1 year of this date and rereleased, or its designation for CME credit will become invalid.

New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Dear Colleague:

If followed for a sufficiently long period, the vast majority of patients with superficial bladder cancer will experience disease recurrence or progression after primary treatment. Immunotherapy with intravesical Bacillus Calmette-Guérin (BCG) shows high efficacy, but dose-limiting toxicity may develop. While intravesical chemotherapeutic agents have demonstrated some decrease in recurrence rate, the effects are generally modest and tumor progression is unaltered. Furthermore, they are also associated with toxicities that at times can be significant. Thus, given the large number of patients with superficial bladder cancer who will experience recurrent or progressive disease and the toxicities associated with BCG and chemotherapy, new, less-toxic options are needed. Intravesical interferon alfa in combination with low-dose BCG is an effective alternative for patients at high risk for disease recurrence or progression whose disease is refractory to standard-dose BCG. In addition, combination therapy may be appropriate for patients who are potential candidates for cystectomy because of prior treatment failure.

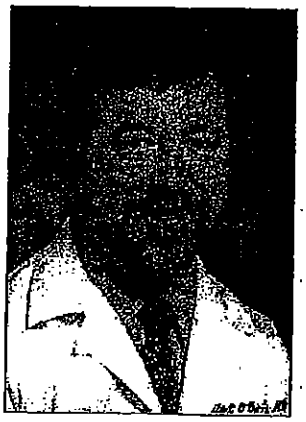
We are pleased to offer you this educational activity, *New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach*, which provides an introduction to the use of interferon alfa in the treatment of superficial bladder cancer. An outstanding faculty of urologists describe patient cases and discuss treatment dilemmas and options. The cases and corresponding discussions provide practical strategies for approaching the management of superficial bladder cancer, especially among the more challenging clinical scenarios.

The goal of this newsletter, the first in a series of four, is to provide you with critical insight into the management of superficial bladder cancer in a patient with recurrent disease for whom radical therapy is medically inappropriate. This case-based activity, which is designated for 1 CME credit upon completion of the four-case series, is designed to update you on the latest findings from clinical trials and the implications for clinical practice.

We hope you find this series helpful and informative.

Sincerely,

Michael A. O'Donnell, MD
Program Chair
Associate Professor and Director of Urologic Oncology
Department of Urology
University of Iowa
Iowa City, IA



Patient Description

The patient is a 79-year-old male who presents with significant urinary frequency, urgency, and moderate dysuria of about six months' duration. He had previously received a two-week course of a fluoroquinolone antibiotic from his primary care physician without clear improvement. He denies fever, chills, flank pain, or gross hematuria. He admits to a moderate decrease in his urinary force of stream, which has remained unchanged over the past year. His medical history is remarkable for two prior diagnoses of myocardial infarction, hypertension, chronic obstructive pulmonary disease, osteoarthritis, and a cerebral vascular accident with minimal motor deficit and mild memory loss. He was treated for tuberculosis 20 years ago. He has no current angina. Medications include atenolol, hydrochlorothiazide, and low-dose aspirin. He has a >50 pack-year history of smoking, but has not used tobacco for the last 15 years. He lives with his 78-year-old wife in an assisted-living facility and has good support from his extended family.

On physical exam, the patient is a thin, but essentially healthy-appearing, elderly man in no apparent distress. Examination of the heart, lungs, and abdomen is unremarkable. The prostate weighs approximately 45 grams and is nontender and without nodules.

(continued on page 2)

Learning Objectives

This case-based educational activity is designed to update urologists on emerging treatment options for patients with superficial bladder cancer.

After participating in this activity, physicians will be better able to:

- Describe the clinical characteristics, staging, and grading of bladder cancer as they relate to clinical decision making
- Discuss the strengths and weaknesses of current treatments for both disease eradication and prevention of recurrence
- Describe the benefits of rIFN-α2b as second-line monotherapy or in combination with BCG, as illustrated in selected case studies
- Apply the lessons learned from the case studies about the use of rIFN-α2b to improve the clinical outcomes of patients with superficial bladder cancer

CME Information

Projects In Knowledge™ is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians.

Projects In Knowledge designates this educational activity for up to 1 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours that he/she actually spent in the educational activity.

This independent CME activity is planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Disclosure Information

The Disclosure Policy of Projects In Knowledge requires that faculty participating in a CME activity disclose to the audience any significant relationship they may have with a pharmaceutical or medical equipment company, product, or service that may be mentioned as part of their presentation, as well as any relationship with the commercial supporter of this activity.

This independent CME activity is supported by an unrestricted educational grant from

Schering ONCOLOGY BIOTECH

This activity may include a discussion of therapies that are unapproved for use or investigational, ongoing research, or preliminary data.

The opinions expressed during this activity are those of the faculty and do not necessarily reflect those of the sponsor or the commercial supporter.

Michael A. O'Donnell, MD, has indicated significant relationships with Eli Lilly and Co, MycImmune, and Schering-Plough.

The urinalysis results reveal 1+ for blood on dipstick and show 1 to 3 red blood cells per high-power field (HPF), 0 to 2 white blood cells per HPF, and no bacteria. Prostate-specific antigen (PSA) level is 4.5 ng/mL, blood urea nitrogen (BUN) level is 24 mg/dL, and creatinine level is 1.5 mg/dL.

Diagnostic Assessment

Question 1:

Which of the following diseases is LEAST likely to account for this patient's condition?

a. Chronic nonbacterial prostatitis
b. Bladder cancer
c. Bladder calculus
d. Renal cell carcinoma
e. Neurogenic bladder

Discussion

(d) With the exception of renal cell carcinoma, any of the conditions listed could account for irritative voiding symptoms. Of the possible diagnoses, bladder cancer should be considered foremost in this patient, because of his age and history of tobacco use. As many as 10% to 20% of patients with bladder cancer present with irritative voiding symptoms, and half of these patients present without significant hematuria. Carcinoma in situ (CIS) is the bladder cancer subtype most commonly associated with these findings.

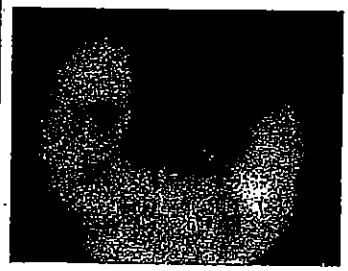


Figure 1. Carcinoma in situ: cystoscopic appearance.

Case Continues

The patient's urine is evaluated, and the cytology result is strongly suspicious for high-grade urothelial carcinoma. The result of an intravenous pyelogram is normal, except for moderate benign prostatic hyperplasia. Cystoscopy under anesthesia reveals patchy, raised, erythematous lesions without frank exophytic or papillary tumors (Figure 1). The histopathology report from the bladder biopsies reads "high-grade severe urothelial dysplasia."

Initial Therapy

Question 2:

What is your initial choice of therapy for this patient?

a. Observation only
b. Repeat bladder biopsies and/or cytologies
c. Mitomycin C intravesical chemotherapy
d. Bacillus Calmette-Guérin (BCG)
e. Radical cystectomy

Discussion

(d) Bacillus Calmette-Guérin is the initial drug of choice. Repeat biopsies are unnecessary, since severe dysplasia and CIS are now considered the same entity, according to a recent Pathology Consensus Conference convened by the World Health Organization and the International Society of Urologic Pathology.[1] Considering that the progression rate for CIS is 50%, observation would not be advisable in this otherwise fully functional elderly man.[2] While mitomycin C may lead to an initial 40% to 50% complete response in patients with CIS, randomized controlled studies have found BCG to be superior, with durable complete responses approaching 60% (Figure 2).[3] Prior history of tuberculosis is not a contraindication to BCG therapy. Radical cystectomy would be premature, and would present an increased risk of complications for this particular patient.

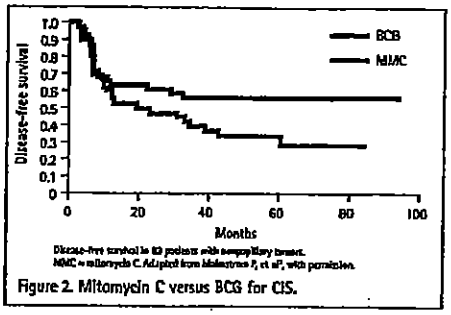


Figure 2. Mitomycin C versus BCG for CIS.

Case Continues

Six weeks after completing a six-week induction course of intravesical BCG, the patient undergoes repeat cytoscopy. Multiple areas of diffuse redness are seen. Bladder wash is positive for high-grade transitional cell carcinoma (TCC). Bladder biopsies reveal multifocal CIS.

Secondary Therapy

Question 3:

What would you recommend for this patient with recurrent CIS?

a. Mitomycin C
b. Repeat BCG
c. Valrubicin
d. Radical cystectomy
e. Systemic chemotherapy with or without radiotherapy

Discussion

(b) A second course of BCG has a 30% to 50% chance of rendering a patient with recurrent CIS disease free.[4] In contrast, a clinical study in which patients failing BCG therapy were crossed over to a mitomycin C regimen found that only 19% remained free of recurrence by three years.[3] In the setting of patients with at least two failures on BCG therapy, valrubicin has demonstrated an initial complete response rate of 21% at six months, but only 8% at two years.[5] Radical cystectomy is still premature in this elderly male with moderate comorbidities. Systemic chemotherapy, with or without radiotherapy, is generally ineffective against CIS.

Case Continues

A second six-week induction course of BCG is initiated. The patient develops significant local cystitis symptoms, intermittent hematuria, low-grade fevers, malaise, and joint aches, but is eventually able to complete therapy. He returns six weeks later for re-evaluation. Results of a voided urine cytology are positive, and the bladder biopsies continue to show multifocal CIS. The patient adamantly refuses cystectomy.

Salvage Therapy

Question 4:

How would you handle this clinical situation?

a. Observe for another three months before deciding
b. Offer a third course of BCG or maintenance three-week miniseries of BCG every three to six months
c. Start intravesical valrubicin
d. Start intravesical interferon alfa
e. Start combination low-dose BCG (one-third strength) plus interferon alfa

Discussion

(e) The patient's disease is refractory to BCG, and he is unable to tolerate further treatment with standard-dose BCG. While approximately 25% of patients with CIS will have a delayed complete response to BCG at six months after primary therapy, this is rarely seen after back-to-back treatment failure.[6] Even if the patient were able to tolerate another course of standard-dose BCG, a third course of BCG has a success rate of less than 20%.[4] Maintenance BCG has not yet been evaluated in this setting. Valrubicin, while appropriate, is prone to causing cystitis and displays a durable response rate of only about 8% at two years (Table 1[3,5,7]).[5] Intravesical interferon alfa monotherapy is less irritating than other agents, but provides only a 12% durable response and is minimally active against BCG-refractory CIS.[8] Combination low-dose BCG plus interferon alfa provides a reasonable alternative to other conservative options, since it has shown a 55% complete response rate.[7] The protocol for this study included six treatments of BCG at one third the standard dose plus 50 million units (MU) of interferon alfa-2b. Three additional three-week miniseries, which included BCG with the dose titrated down by one-third increments as needed for tolerance, were given at 3, 9, and 15 months after the last induction dose. A reinduction arm with one tenth the standard BCG dose plus 100 MU interferon alfa was included for patients who showed an incomplete response to the first induction cycle.

Case Continues

Treatment is initiated with BCG at one third the standard dose plus 50 MU of interferon alfa. After the second treatment, the patient experiences moderate urinary symptoms, which resolve slowly over five days.

Table 1. Efficacy Comparison of Agents After BCG Failure

Author	Agent	Patient Group	N	2-year NED(%)
Catalona[4]	BCG, 3rd course	Mixed	6	20
Williams[6]	IFNα	CIS-pure	34	12
Malmstrom[7]	MMC	Mixed[a]	19	23
Steinberg[5]	Valrubicin	CIS[b]	90	8
O'Donnell[3]	BCG + IFNα	Mixed[b]	21	55

[a] For BCG failures x 1; crossover
[b] All concurrent papillary TCC resected
[c] For BCG failures x 2+

NED = no evidence of disease; MMC = mitomycin C; IFNα = interferon alfa; mixed = patients with T_a, T_1, or CIS tumors; CIS-pure = patients with primary CIS tumors without papillary TCC

Improving Treatment Tolerance

Question 5:

What step(s) should you take to increase the likelihood that the patient can tolerate this treatment regimen? (Select all that apply.)

a. Provide urinary analgesics and antispasmodics as appropriate
b. Delay dosing interval for two to three weeks
c. Reduce BCG dose sequentially as needed, from 1/3 to 1/10, 1/30, or 1/100
d. Reduce interferon alfa dose
e. Add three days of oral isoniazid, beginning the day prior to planned treatment

Discussion

(a), (b), and (c) may help the patient tolerate BCG plus interferon alfa combination therapy. A reduction in BCG dose, titrated to tolerance; a delay in dosing interval; and appropriate use of urinary analgesics and antispasmodics (even pretreatment narcotics) have allowed BCG-intolerant patients to continue with therapy and achieve high therapeutic success with the combination regimen.[7] (d) and (e) are unlikely to decrease local side effects and may actually compromise efficacy. While interferon alfa is tolerated at intravesical doses up to 1000 MU/week, it induces minimal cystitis.[8] Oral isoniazid therapy has been shown to reduce neither local nor systemic toxicity from BCG.[9]

Epilogue

This case study is based on an actual patient with multifocal CIS who had sequentially failed two courses of BCG. He had a dramatic response to low-dose BCG plus interferon alfa combination therapy, with complete resolution of cytologic and histologic evidence of CIS. Based on the SWOG 8507 study of miniseries maintenance,[6] two maintenance miniseries of very low-dose BCG and interferon alfa were given at three and six months. However, the patient eventually developed intolerance, necessitating discontinuation. He remained disease free for 2 1/2 years, but died following a hip fracture. At the time of his death, the patient had no evidence of recurrent TCC.

Summary

While BCG remains the mainstay of treatment for CIS, many patients eventually fail BCG therapy, and the appropriate next course of action is a dilemma. Intravesical chemotherapy is generally a poor alternative to BCG, because of low durable response rates. Patients failing BCG therapy for the first time can be re-treated with BCG with a reasonable chance of success. However, tolerance is often a problem, especially at the standard BCG dose. Indeed, recent clinical studies suggest that lower BCG doses may actually be more effective than higher doses for BCG-sensitized patients.[10,11]

After a second BCG failure, cystectomy is generally considered unless medically contraindicated. Interferon alfa monotherapy can be used as salvage therapy in a small percentage of these patients, but is most effective for patients who have relapsed beyond six months.[8] In early trials, BCG plus interferon alfa combination therapy appears promising when compared with BCG alone, for initial treatment and as an option for "salvaging" BCG-refractory patients.[7,11,12] A biologic basis for immune synergy has also been firmly established.[13] However, until confirmed in larger studies, BCG and interferon alfa combination therapy might best be reserved for high-risk patients for whom radical therapy is medically inappropriate. In addition, it may also be appropriate in place of standard BCG in cases where the next step after that BCG failure would otherwise be radical therapy

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13. Luo Y, Chen X, Downs TM, DeWolf WC and O'Donnell MA. IFN-alpha 2B enhances Th1 cytokine responses in bladder cancer patients receiving Mycobacterium bovis bacillus Calmette-Guerin immunotherapy. *J Immunol.* 1999;162:2399-2405.

CME Posttest

New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Release Date: April 30, 2001

CME Instructions

During the next 24 weeks you will receive a total of 4 newsletters. To receive documentation of your participation in this 4-part CME activity for a total of 1 hour of CME credit, please complete the following steps:

1. Read each newsletter.
2. Complete the CME posttest included in each of the newsletters.
3. Mail or fax each of the completed posttests to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.*
4. After reading the final newsletter, complete the CME evaluation survey contained therein.
5. Mail or fax your posttest and the CME evaluation survey to Projects In Knowledge (address above).

*At the end of the series, Projects In Knowledge will mail you an acknowledgment of your participation in this activity if your combined score for all four posttests is 70% or better. If your combined score is lower than 70%, you will be notified by mail and will be given an opportunity to take a single test covering information from all four issues of the newsletter.

Name _____ Degree _____

Mailing Address _____

City _____ State _____ ZIP _____

Phone # _____ Fax # _____

E-mail _____

Please indicate your answers below (circle one).

1. Irritative voiding symptoms may often be seen in patients with:
   a. Renal cell carcinoma
   b. Bladder cancer
   c. Bladder calculus
   d. Both b and c

2. Carcinoma in situ is:
   a. Associated with a progression rate of 10%
   b. Associated with a progression rate of 50%
   c. Distinct from severe dysplasia
   d. Both b and c

3. For patients with recurrent CIS after a single course of intravesical BCG:
   a. A second course of BCG has a 30% to 50% chance of rendering the patient disease-free
   b. A course of mitomycin C has only a 19% remission rate at three years
   c. Without further therapy, there is an approximately 25% risk of delayed complete response to BCG by six months
   d. All of the above

4. Combination therapy with low-dose BCG plus interferon alfa:
   a. May be better tolerated with a reduced BCG dose
   b. Is rarely associated with cystitis
   c. May be better tolerated with oral isoniazid prior to planned treatment
   d. Has shown a 5% complete response rate

1531A

Education Initiative in Urology

THE TREATMENT REPORTER UROLOGY

Release Date: This is the second part of a four-part series having an original release date of April 30, 2001. This newsletter has been planned, produced, and approved as a CME activity in accordance with the Essentials and Standards for Commercial Support. This enduring activity will be reviewed within 18 months of the original release date and rereleased, or its designation for CME credit will become invalid.

New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Dear Colleague:

Immunotherapy with intravesical Bacillus Calmette-Guérin (BCG) is considered the gold standard for initial treatment of superficial bladder cancer. However, approximately 30% of patients treated with the agent will develop persistent or recurrent disease. Management of patients with persistent or recurrent disease should include consideration of various therapeutic options. Intravesical interferon alfa is one such option. As monotherapy, interferon alfa has shown salvage rates as high as 66% in patients with BCG-refractory carcinoma-in-situ. In addition, recent data suggest that the combination of BCG and interferon are associated with response rates of up to 65% at one year.

We are pleased to offer you this educational program, *New Prospects in the Treatment of Superficial Bladder Cancer*, which provides a case-based introduction to the use of interferon alfa in the treatment of superficial bladder cancer. An outstanding faculty of urologists describe patient cases and discuss treatment dilemmas and options. The cases and corresponding discussions provide practical strategies for approaching the management of superficial bladder cancer, especially among the more challenging clinical scenarios.

The goal of this newsletter, the second in a series of four, is to provide you with critical insight into the management of superficial bladder cancer in a patient with persistent low-grade transitional cell carcinoma of the bladder. This case-based program, which is designated for 1 CME credit upon completion of the four-case series, is designed to update you on the latest findings from clinical trials and the implications for clinical practice.

We hope you find this series helpful and informative.

Sincerely,

Michael A. O'Donnell, MD
CME Activity Chair
Associate Professor and Director of Urologic Oncology
Department of Urology
University of Iowa
Iowa City, IA

Leonard G. Gomella, MD
Bernard W. Godwin Associate Professor of Prostate Cancer
Director, Urologic Oncology
Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA

Patient Description

The patient is a 54-year-old male who presents with a 1-month history of intermittent, painless, gross hematuria. The patient has no significant past medical history except an inguinal hernia repair at age 45. He stopped smoking 10 years ago and is an auto mechanic. He describes mild nocturia, voiding once or twice nightly. Physical examination is unremarkable.

Evaluation includes an excretory urogram, urine culture, urinary cytology, and cystoscopy. The urogram reveals a bifid renal pelvis on the left, with the suggestion of a filling defect on the left bladder base. Urine culture is negative. Cytology is suspicious for low-grade transitional cell carcinoma (TCC). A 2-cm lesion is found at the left bladder base behind the trigone, with several smaller papillary lesions near the left bladder neck. The patient undergoes a transurethral resection of the bladder tumor (TURBT) with random bladder biopsies. Pathology is consistent with multifocal Ta grade 1-2 TCC. There is no carcinoma-in-situ (CIS), but mild dysplasia is observed in two of the random biopsies. The TUR specimen of the large tumor includes the muscularis propria. p53 staining of the specimen is negative.

(continued on page 2)

Learning Objectives

This case-based educational activity is designed to update urologists on emerging treatment options for patients with superficial bladder cancer.

After participating in this activity, physicians will be better able to:

- Describe the clinical characteristics, staging, and grading of bladder cancer as they relate to clinical decision making
- Discuss the strengths and weaknesses of current treatments for both disease eradication and prevention of recurrence
- Describe the benefits of rIFN-α2b as second-line monotherapy or in combination with BCG, as illustrated in selected case studies
- Apply the lessons learned from the case studies about the use of rIFN-α2b to improve the clinical outcomes of patients with superficial bladder cancer

CME Information

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This activity may include a discussion of therapies that are unapproved for use or investigational, ongoing research, or preliminary data.

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Leonard G. Gomella, MD, has indicated a significant relationship with Schering Oncology/Biotech.

Michael A. O'Donnell, MD, has indicated significant relationships with Eli Lilly and Co, MycImmune, and Schering-Plough.

Initial Assessment

Question 1:

This patient is considered a candidate for initial intravesical therapy based on which adverse feature of his bladder tumor?

a. Mild dysplasia is present in two of the random biopsies
b. Ta disease is present
c. Multifocal TCC is found on initial presentation
d. p53 staining of the specimen is negative
e. This is a low-grade bladder cancer, and thus intravesical therapy is not indicated

Discussion

(c) Intravesical therapy can eradicate existing tumors, prevent progression and recurrence, and is recommended for patients at high risk for recurrence or progression. However, not all patients with superficial TCC require intravesical therapy (Table 1). Multifocality indicates a higher degree of urothelial instability, which translates into higher recurrence rates. The 1-year recurrence rates of 22%, 48%, and 75% for patients with one, two, and three or more tumors, respectively, have been reported.[1] Mild dysplasia and Ta disease are not considered adverse features of TCC.[2,3] p53 positive staining, reflecting abnormal p53, is associated with higher rates of progression to muscle invasion. This patient presents with multifocal low- to intermediate-grade cancer, thus there is a potential role for intravesical therapy.

Table 1. Indications for intravesical therapy in patients with superficial TCC of the bladder.

- Multiple, diffuse papillary tumors
- Large tumor (>2 cm) at initial presentation
- Tumor recurrence within 1 year of treatment
- Ta grade 3
- Any T1 tumor, regardless of grade
- Presence of CIS (severe dysplasia)
- Positive urine cytology after resection of visible tumor

Case Continues

Due to the presence of multifocal disease, a 6-week course of Bacillus Calmette-Guérin (BCG) is initiated 14 days after the procedure. The patient tolerates the treatment well, experiencing only mild irritative voiding symptoms and malaise for 24 hours following each instillation. Repeat cystoscopy with biopsy is performed 4 weeks following the last BCG instillation. The cystoscopic findings include diffuse mucosal erythema and a reddish raised lesion in the center of the scar from the previous 2-cm tumor. Urinary cytology is negative. The biopsies from the erythematous regions reveal only chronic inflammatory changes. The deep biopsy of the previous tumor site shows persistent grade 2 Ta disease.

Secondary Management

Question 2:

In patients with persistent low-grade TCC following an initial course of BCG, the most reasonable strategy is:

a. Immediate cystectomy
b. Bilateral retrograde pyelograms with brush biopsies of both renal pelves
c. Intravesical chemotherapy
d. A repeat 6-week course of BCG
e. Monthly maintenance BCG for 1 year

Discussion

(d) A single 6-week course of BCG may be inadequate, but some nonresponders may require an additional course of BCG before moving to salvage therapies. Seventy percent of patients treated with a second 6-week course remain tumor free for up to a year compared with 35% of patients treated with a single

6-week course of BCG, suggesting that another course of BCG is appropriate.[4] A SWOG study that compared a single 6-week course of BCG with a 6-week course followed by an additional 3-week course at 3 months found a significant 25% complete response rate in the group treated with the additional 3 weeks of BCG.[5] Radical cystectomy is not indicated at this point since there is no evidence of progression in stage or grade and no evidence of disease invasive to the muscle. Upper-tract studies are not needed since the result of the initial upper-tract imaging was negative, and recent urinary cytology finding is negative. Intravesical chemotherapy has not proven to be consistently effective after a failed course of BCG and maintenance will not convert a nonresponder into a responder.

Case Continues

A second 6-week course of BCG is given. A posttreatment biopsy of the bladder shows several new small tumors surrounding the left ureteral orifice. A retrograde pyelogram is unremarkable except for the bifid renal pelvis. The patient has no specific urologic complaints. The pathologic specimen shows multifocal, low-grade Ta, grade 1–2 TCC. The patient is concerned about the possibility of invasive bladder cancer, and a computed tomography scan of the abdomen and pelvis is ordered. Results of the procedure are completely normal, with no evidence of bladder wall thickening. The patient declines an offer for referral to a local cancer center for investigational protocols.

Management of Refractory Superficial Bladder Cancer

Question 3:

Which statement is true about a patient with low-grade, low-stage superficial bladder cancer who has failed two 6-week cycles of BCG?

a. Intravesical chemotherapy with mitomycin C is the standard of care and can achieve salvage rates of over 50%

b. Interferon alfa-2b, either alone or in combination with BCG, has been reported to have response rates between 25% and 50% in patients with BCG-refractory disease

c. A third course of BCG should be attempted, using an alternate strain

d. Intravesical valrubicin is indicated in all patients with BCG-refractory disease

e. Immediate cystectomy is indicated

Discussion

(b) As intravesical monotherapy, interferon alfa-2b has shown activity with a low-toxicity profile. Salvage rates as high as 66% have been reported for patients relapsing with CIS following BCG treatment, with lower rates (25%–40%) for patients with papillary disease.[6] Recent data suggest that the combination of BCG and interferon alfa is synergistic, with response rates of up to 65% at 1 year.[7,8] While not FDA approved for this use, the *US Pharmacopeia* lists interferon alfa as second-line therapy in superficial bladder cancer.

Although BCG is arguably the "gold standard" for superficial bladder cancer, recurrences are reported in up to 30% of patients. Herr et al reported a progression rate of 38% and disease-specific mortality rate of 25% in BCG-treated patients who were followed for 10 years.[8] The BCG strains used today were originally derived from the Pasteur strain developed by Albert Calmette and Camille Guérin in the late 19th century. Several other strains have been developed with differing biological activity, which could result in different levels of efficacy. All FDA-approved BCG strains have been shown to be effective in the management of superficial TCC, but there are no data to support administration of a third course of BCG using an alternate strain.

Valrubicin, an adriamycin analogue, is the only FDA-approved regimen for BCG-refractory bladder cancer,[10] with a reported response rate of 21%. Valrubicin is indicated for intravesical therapy of BCG-refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality. Standard intravesical chemotherapy (mitomycin C) has not been shown to be a reliably effective salvage therapy in patients failing BCG.[2]

Radical cystectomy is indicated for refractory, diffuse, high-grade T1 lesions, CIS, or tumors with prostatic stromal involvement. It is also recommended for patients with T1 grade 3 TCC refractory to BCG.[11] This patient has low-risk bladder cancer; additional salvage therapies should be attempted. If the patient demonstrates progression to a higher grade or stage (ie, T1 G3), immediate cystectomy or a bladder preservation protocol should be offered.

Case Continues

The patient receives 6 weeks of intravesical mitomycin C at a dose of 40 mg. Follow-up cystoscopy and biopsy demonstrate two new papillary lesions on the left lateral wall. Results of random biopsies are negative. Pathologic examination

again demonstrates a Ta grade 2 TCC. Having failed two cycles of BCG and mitomycin-C, the patient is treated with intravesical interferon alfa-2b for 6 weeks at a dose of 100 million units in 50 cc sterile water. The patient reports mild malaise after each instillation, but no lower-tract symptoms. Cystoscopy and bladder biopsy specimens demonstrate no visible lesions, and histologic examination of biopsy specimens shows areas of denuded mucosa, but no cancer.

Follow-up of Superficial TCC

Question 4:

What is the recommended follow-up protocol for patients with successfully treated superficial TCC of the bladder?

a. Cystoscopic follow-up is not needed for low-risk bladder cancer
b. Urinary cytology, with cytoscopy and biopsy only if the cytology is positive
c. Cystoscopy and cytology every 3 months for 2 years, then every 6 months
d. Urinary tests, such as NMP-22 or BTA STAT, every 3 months for 2 years, then every 6 months
e. Monthly cystoscopy and cytology for life

Discussion

(c) The follow-up protocol recommended for patients with superficial TCC includes cystoscopy and urine cytology every 3 months for 2 years, then every 6 months for 2 years, and then yearly thereafter. Annual excretory urography is also recommended, although this recommendation is not uniformly accepted.

Whether or not to continue long-term cystoscopic surveillance for low-grade papillary tumors is disputed. The annual incidence of first recurrence declines rapidly in the first 2 years but remains steady for up to 8 years.[12] While some experts recommend continued cytoscopic surveillance, others suggest stopping cystoscopy after 5 years if there has been no recurrence.[13] As demonstrated by this patient, most superficial low-grade papillary tumors will have recurrences of the same grade and stage.

Urine cytology has a low sensitivity in diagnosing low-grade tumors. The use of newer urinary tests, such as BTA-Stat and NMP-23, may improve detection rates or alter our standard follow-up, but these tests need further validation.

Data from Sloan-Kettering that included a 15-year follow-up period showed that patients with high-risk tumors may progress at a later time.[14] Investigators found a high incidence (21%) of upper-tract tumors in patients with high-grade bladder lesions. These upper-tract tumors developed after an average of 7.3 years. Patients with high-grade superficial TCC should have continued upper-tract surveillance. The value of upper-tract surveillance for patients with lower-grade cancer is disputed.

Conclusions

The management of superficial bladder cancer continues to progress, leading to improved outcomes for patients with the disease. TUR with intravesical BCG is considered the gold standard, but approximately 30% of patients undergoing this regimen will have persistent or recurrent disease. Salvage therapies for patients with BCG-recurrent disease continue to improve, with a growing interest in combination immunotherapies and intravesical gene therapies.[2, 8, 15, 16] The ongoing efforts to find a uniformly reliable predictor of therapeutic response and alternative therapies to lower toxicity but not efficacy will continue to improve the management of superficial bladder cancer.

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CME Posttest

New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Original Release Date: April 30, 2001

CME Instructions

Over a period of 24 weeks you will receive a total of 4 newsletters. To receive documentation of your participation in this 4-part CME activity for a total of 1 hour of CME credit, please complete the following steps:

1. Read each newsletter.
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3. Mail or fax each of the completed posttests to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.*
4. After reading the final newsletter, complete the CME evaluation survey contained therein. All four posttests and the evaluation must be received by October 30, 2002, for you to be eligible to receive CME credit.
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*At the end of the series, Projects In Knowledge will mail you an acknowledgment of your participation in this activity if your combined score for all four posttests is 70% or better. If your combined score is lower than 70%, you will be notified by mail and will be given an opportunity to retake the test.

Name _____ Degree _____

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E-mail _____

Please indicate your answers below (circle one).

1. Intravesical therapy:
   a. Is indicated for all patients with superficial TCC
   b. Can eradicate existing tumors.
   c. Can prevent progression
   d. Both b and c

2. Which is true about the use of BCG for low-grade TCC?
   a. A single 6-week course is generally adequate therapy
   b. A second course of BCG does not improve tumor-free rates
   c. Once a patient has failed BCG, radical cystectomy should be performed
   d. Persistent low-grade TCC can be treated with additional courses of BCG

3. Which is FALSE about interferon alfa-2b?
   a. The combination of BCG and interferon alfa-2b appears to be synergistic
   b. The response rate for combination therapy with BCG and interferon alfa is approximately 13% at 1 year
   c. Salvage rates with interferon alfa-2b monotherapy are as high as 66% for patients with CIS failing prior BCG treatment
   d. The *US Pharmacopeia* lists interferon alfa as second-line therapy in superficial bladder cancer

4. Which is true about recommended follow-up for patients with successfully treated superficial TCC?
   a. Excretory urography is clearly indicated every year
   b. Urine cytology has a high sensitivity in diagnosing low-grade tumors
   c. The recommended timing for follow-up cytoscopy and cytology is every 3 months for 2 years, every 6 months for 2 years, then yearly thereafter
   d. Urinary tests, including NMP-23, are recommended annually for follow-up

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Education Initiative in Urology

THE TREATMENT REPORTER UROLOGY

Release Date: This is the third part of a four-part series having an original release date of April 30, 2001. This newsletter has been planned, produced, and approved as a CME activity in accordance with the Essentials and Standards for Commercial Support. This enduring activity will be reviewed within 18 months of the original release date and rereleased, or its designation for CME credit will become invalid.

New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Dear Colleague:

Treating patients with recurrent low-grade, low-stage transitional cell carcinoma (TCC) of the bladder presents a significant challenge for urologists. Controversies regarding the use of adjuvant intravesical therapy for these patients arise because of the potential toxicities of therapeutic agents despite their documented efficacy. Thus, management of recurrent low-grade TCC requires a thorough understanding of the available treatment options to optimize prevention of disease progression and recurrence while minimizing risk of toxicities. Intravesical interferon alfa is a viable treatment option for patients who cannot tolerate frequently occurring side effects seen with other intravesical agents.

We are pleased to offer you *New Prospects in the Treatment of Superficial Bladder Cancer*, a CME newsletter addressing the use of interferon alfa in the treatment of recurrent low-grade superficial bladder cancer. This case-based CME activity presents the case of a surgeon with recurrent low-grade, low-stage TCC who requires adjuvant therapy to enable him to sustain his professional work in the operating room. It provides practical strategies for approaching this management dilemma and updates you on the latest findings from clinical trials and their implications for clinical practice.

This newsletter is the third in a series of four. Physicians can receive 1 hour of CME credit upon completion of the four parts. It is designed to provide you with critical information that will translate into practical clinical application. Don't miss this opportunity to gain the knowledge you can in turn offer your patients so that they may improve their quality of life.

We hope you find this series helpful and informative.

Sincerely,

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Patient Description

The patient is a 62-year-old male surgeon, and a colleague of mine who stopped me in the hospital locker room to report an episode of painless gross hematuria. After completing his surgical case, he voided a full stream of painless gross hematuria. By the next void, his urine had cleared. He also admitted to urgency. He has no prior history of stone disease or urologic abnormalities.

His past medical history is significant for cigarette smoking (>40 pack-years), and he still smokes occasionally. He was purified protein derivative (PPD) positive in medical school and was treated for one year with isoniazid. His surgical history is positive for a prior cholecystectomy and for a splenectomy after trauma.

His physical exam reveals a normal healthy-appearing male. Examination of his head, neck, and chest is negative. His abdomen is benign to palpation. Two old surgical scars are seen. His bladder is nonpalpable. Testes are descended, without any evidence of intrascrotal masses or tenderness. The prostate is benign, without any evidence of fluctuance; it is nontender, and no nodules

(continued on page 2)

Learning Objectives

This case-based educational activity is designed to update urologists on emerging treatment options for patients with superficial bladder cancer.

After participating in this activity, physicians will be better able to:

- Describe the clinical characteristics, staging and grading of bladder cancer as they relate to clinical decision making
- Discuss the strengths and weaknesses of current treatments for both disease eradication and prevention of recurrence
- Describe the benefits of rIFN-α2b as second-line monotherapy or in combination with BCG, as illustrated in selected case studies
- Apply the lessons learned from the case studies about the use of rIFN-α2b to improve the clinical outcomes of patients with bladder cancer

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Steven L. Cohen, MD, has indicated significant relationships with Merck & Co, Inc, Pfizer Inc, and Schering.

Michael A. O'Donnell, MD, has indicated significant relationships with Eli Lilly and Co, MycImmune, and Schering-Plough.

are palpated. It weighs approximately 30 g and is 1+ enlarged. The blood urea nitrogen (BUN) is 19 mg/dL and the creatinine 0.9 mg/dL. Prostate-specific antigen (PSA) is 0.6 ng/mL.

Initial Assessment

Question 1:

Which one of the following diseases is most likely in this patient?

a. Bladder stone with obstruction
b. Bladder cancer
c. Ureteral calculus
d. Chronic retention with urinary tract infection (UTI)
e. Bacterial prostatitis

Discussion

(b) Bladder cancer is frequently associated with painless, gross or microscopic hematuria. In fact, this presentation is seen in approximately 85% of patients.[1] The fact that this patient has a long history of smoking increases his risk of bladder cancer. Given the lack of previous urologic voiding problems, UTIs and retention are much less likely. The absence of flank pain and colic make ureteral calculus less of a probability. Bacterial prostatitis is generally associated with lower urinary tract symptoms.

Case Continues

The laboratory urinalysis (UA) reveals 6–10 red blood cells per high power field (HPF), 1–2 white blood cells per HPF, and negative urine cultures. Cytology is 'atypical.' An intravenous pyelogram reveals normal upper tracts with a small postvoiding residual, and a possible 2-cm filling defect on the posterior wall of the bladder.

Cystoscopy under anesthesia reveals a single 2.5-cm papillary bladder tumor on the right posterior wall. A transurethral resection of the bladder tumor (TURBT) reveals a Ta grade 2 transitional cell carcinoma (TCC). Postoperative course is uneventful.

Initial Management

Question 2:

Which indication does NOT require immediate intravesical adjuvant therapy?

a. Noninvasive Ta grade 3 TCC
b. Multiple (more than 2) Ta grade 2 lesions
c. Single, superficial, Ta low-grade tumor
d. History of recurrent, multiple, grade-1 lesions within the past 3 years

Discussion

(c) The indication for intravesical therapy is based on the risk of progression and recurrence, which is correlated with tumor multiplicity, size, stage, and grade.[2,3] Low-grade disease may be well controlled by TUR only.[4] Therefore, "C" is the correct answer.

Case Continues

No intravesical therapy is given. At six-month follow-up, the cystoscopy is negative. At one-year follow-up, the cystoscopy reveals three small papillary tumors posteriorly at the junction of the old scar, and two other lesions measuring 1.5 cm on the left lateral wall. Postresection pathology reveals all to be Ta grade 2 tumors.

Table 1. Toxicity of Intravesical BCG

Minor (%)		Major (%)	
Cystitis	91	Temperature >39.5°C	3
Hematuria	43	Granulomatous prostatitis	1
Fever, low grade	29	Major hematuria	1
Malaise	24	Hepatitis/pneumonitis	0.7
Nausea	5	Arthritis	0.5
		Epididymitis-orchitis	0.4
		Sepsis	0.4
		Ureteral obstruction	0.3
		Contracted bladder	0.2

Lamm DL, Steg A, Boccon-Gibod L, et al. Complications of Bacillus Calmette-Guerin immunotherapy: a review of 2602 patients and comparison of chemotherapy complications. *Prog Clin Biol Res.* 1989;310:335–355.

Recognizing that his disease is now multifocal, we discuss the need for adjuvant intravesical therapy. I recommend Bacillus Calmette-Guérin (BCG). My colleague researches BCG on the Internet. Understanding the toxicity of BCG, he realizes that severe cystitis would interfere with his work, since severe urgency or frequency would not allow him to complete a cholecystectomy.

Secondary Management

Question 3:

What would you recommend for the treatment of this patient with recurrent tumor?

a. Full-dose BCG
b. Reduced-dose BCG (1/10 dose only)
c. Mitomycin C
d. Radical cystectomy
e. No therapy, observation only

Discussion

(c) With recurrence and multifocality, his risk of progressive disease is increased. Therefore, observation only is not warranted.[3] Because the patient has superficial, completely resectable disease, radical cystectomy would be premature at this time. Reduced-dose BCG requires an additive immunomodulator, interferon alfa, to maintain its efficacy.[5] As shown in Table 2, full-dose BCG is more effective than mitomycin C. However, full-dose BCG is associated with greater toxicities,[5,7] and is not recommended for this particular patient. Therefore, the correct answer is "C."

Case Continues

Concerned about recurrences within one year and multifocality, he agrees to adjuvant therapy. Due to the BCG toxicity profile, he elects mitomycin C therapy.

After induction with mitomycin C, interval cystoscopy reveals one small 0.5-cm papillary tumor, Ta grade 2. Immediately after completion of the TUR, 40 mg mitomycin C and 50 cc sterile saline are placed into the bladder at the time of TURBT, thereby reducing the risk of reimplantation recurrence.[6]

By his second maintenance dose of mitomycin C, my friend is voiding with intermittent hematuria between each of his operating-room cases. Follow-up cystoscopy is negative but, given his symptoms, he wants to consider the option of a sole agent with demonstrated TCC activity but minimal, easily treatable side effects.

Maintenance Therapy

Question 4:

Which agent would you recommend for this patient for maintenance therapy?

a. Full-dose BCG
b. Reduced-dose BCG (1/10 dose only) monotherapy
c. Mitomycin C
d. Interferon alfa
e. Doxorubicin

Discussion

(d) Interferon alfa has demonstrated TCC activity, and yet may have minimal, easily treatable side effects.[8] As outlined in Table 3, there is generally no dose-limiting

Table 2. Number of Patients Without Tumor Recurrence ≥1 Year After Prophylactic Intravesical Therapy Plus Transurethral Resection

Drug	Patients	Control (%)	Treated (%)	Net Benefit (%)
Thiotepa	757	156/327 (48)	243/430 (56)	8
Doxorubicin	860	176/297 (59)	391/563 (69)	10
Mitomycin C	880	170/371 (46)	296/509 (58)	12
BCG	273	48/157 (30)	116/161 (72)	42

Herr HW. Transurethral resection and intravesical therapy of superficial bladder tumors. *Urologic Clinics of N. America.* 1991;1833:526.

toxicity up to 1,000 million units (MU) per dose. Full-dose BCG is an option, but the risk of adverse reactions (listed in Table 1) excludes this as an acceptable option for a patient who wants to continue his work as a surgeon. Reduced-dose BCG monotherapy has no data to support its efficacy. Mitomycin C and doxorubicin share a similar effectiveness and toxicity profile. Since hematuria has already developed with mitomycin C, doxorubicin would not be a beneficial choice for this patient. Therefore, high-dose interferon alfa (100 MU per dose) is a reasonable option, because of the low risk of adverse events and easily treatable side effects.

Case Continues

The patient is maintained on intravesical interferon alfa at 100 MU in 40 cc sterile saline as maintenance therapy. He is currently tumor-free, can finish a colectomy without symptoms, and the urinals remain clean.

Summary

Low-grade, low-stage disease is the most common form of bladder cancer the clinician will see. Certainly, with small-volume disease that is noninvasive and nonprogressive, TURBT management alone is effective and reasonable.[4] Concern for implanting cancer cells on injured mucosa has always been considered, and recent work suggests that single-dose chemotherapy at the time of TURBT reduces the risk of rapid recurrence.[7]

BCG is known to be approximately 50% effective overall in delaying recurrence and progression.[9] The price one pays is a very significant and severe morbidity profile. For my patient, this profile was unacceptable, and a less toxic agent with a minimal side-effect profile was needed. Interferon alfa is associated with cystitis toxicity in approximately 10% of patients,[10] but these symptoms are easily controlled with local effective agents and nonsteroidal anti-inflammatory drugs (NSAIDs). Due to the morbidity profile of BCG and chemotherapy, patients with low-grade, low-stage disease may find interferon alfa, with its more benign toxicity profile, a viable option with minimal risk.

Table 3. Toxicity of Intravesical Interferon alfa

- Most common: "flulike" symptoms, fever
- Incidence 0%–19% in large studies
- No dose-limiting toxicity up to 1,000 MU/dose
- Side effects easily controlled with NSAIDs

Belldegrun AS, Franklin JR, O'Donnell MA, et al. Superficial bladder cancer: the role of interferon-alfa. *J Urol.* 1998:159:1793-1801.

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CME Posttest

New Prospects in the Treatment of Superficial Bladder Cancer: A Case-based Approach

Original Release Date: April 30, 2001

CME Instructions

Over a period of 24 weeks you will receive a total of four newsletters. To receive documentation of your participation in this four-part CME activity for a total of 1 hour of CME credit, please complete the following steps:

1. Read each newsletter.
2. Complete the CME posttest included in each of the newsletters.
3. Mail or fax each of the completed posttests to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.*
4. After reading the final newsletter, complete the CME evaluation survey contained therein. All four posttests and the evaluation must be received by October 30, 2002, for you to be eligible to receive CME credit.
5. Mail or fax your posttest and the CME evaluation survey to Projects In Knowledge (address above).

*At the end of the series, Projects In Knowledge will mail you an acknowledgment of your participation in this activity if your combined score for all four posttests is 70% or better. If your combined score is lower than 70%, you will be notified by mail and will be given an opportunity to retake the test.

Name _____ Degree _____

Mailing Address _____

City _____ State _____ ZIP _____

Phone # _____ Fax # _____

E-mail _____

Please indicate your answers below (circle one).

1. Bladder cancer typically presents with:
   a. Slow stream
   b. Flank pain
   c. Hematuria
   d. Fever

2. CIS or Grade 3 non-invasive TCC is appropriately treated by:
   a. Immediate cystectomy
   b. Systemic chemotherapy
   c. Radiation therapy
   d. Intravesical therapy

3. Side effects of intravesical interferon alfa include:
   a. Sepsis
   b. Flulike symptoms
   c. Hemorrhagic cystitis
   d. Contracted vesical volume

4. Patients who are immunocompromised or completely intolerant of intravesical BCG have no intravesical therapeutic option and should proceed to immediate cystectomy for CIS and/or Ta Grade 3 TCC:
   a. True
   b. False

1531C

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FACULTY PLANNING MEETING

THE ROLE OF INTERFERON ALFA IN SUPERFICIAL BLADDER CARCINOMA ADVISORY BOARD MEETING SERIES

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FACULTY PLANNING MEETING

September 28, 2001

OBJECTIVES

The objectives of today's faculty planning meeting are:

- To review and finalize the advisory board series slide kit
- To review, discuss, and consider pertinent bladder cancer cases for inclusion in the advisory board series content
- To establish learning objectives, agenda, and content outline for the advisory board series

AGENDA

10:30 AM	Continental breakfast	
11:00 AM	Welcome	Mary Naughton Dr. Leonard Gomella
11:05 AM	Overview of bladder cancer advisory board series	Projects In Knowledge
11:15 AM	Review of slide kit and cases	Faculty
12:30 PM	Working lunch	
1:00 PM	Finalize slide kit review	Faculty
1:30 PM	Advisory board series content development	Faculty
2:30 PM	Reimbursement issues	Mary Naughton
2:45 PM	Adjourn	

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THE ROLE OF INTERFERON ALFA IN SUPERFICIAL BLADDER CARCINOMA ADVISORY BOARD MEETING SERIES

ABOUT THIS SERIES

The purpose of the 6 advisory board meetings is to provide participants with practical information on the use of Intron A + BCG in combination for the treatment of superficial bladder cancer and to gather their perspectives on care based on their direct clinical experience.

MEETING FORMAT

Each advisory board meeting will be 4 hours in length. They are scheduled for 6 Saturdays between November 17 and December 8.

- Start time: 10:00 AM; end time: 2:00 PM
- Continental breakfast will be provided
- A working luncheon will be provided
- 20 local urologists will be in attendance
- Two speakers will present, with a local urologist host participating in discussion and question-and-answer sessions
- Content presented will be that developed by the faculty at the September 28 planning meeting
- Speaker honorarium: $2000

MEETING DATES/LOCATIONS

We will request availability of planning meeting faculty, as well as additional series speakers (see page 1 of your meeting binder) for the following tentative dates/cities:

Saturday, November 17:	Absecon, NJ Aptos, CA
Saturday, December 1:	Ft. Lauderdale, FL Farmington, PA
Saturday, December 8:	Marina del Rey, CA San Antonio, TX

The Role of Interferon alfa in Superficial Bladder Cancer

This ~~slide kit~~ presentation contains discussion of investigational uses of agents that are not indicated by the US Food and Drug Administration. Please refer to the official prescribing information for each product for discussion of indications, contraindications, and warnings.

Bladder Cancer: Background

- More than 54,000 new cases/year (US); >12,000 deaths/year
- 4th most common malignancy in men (8th in women)
- Disease prevalence >500,000 (US)
- Average age of onset: 68 years
- Recurrence rate >60%; progression rate ~ 25% despite conventional cystoscopic surgery

Bladder cancer is the fourth most common malignancy in men and the second most common urologic malignancy in the United States; approximately 54,000 new cases are diagnosed annually in the United States, and >12,000 deaths occur annually from bladder cancer.[1] More than 500,000 patients in the United States are currently living with bladder cancer. Nearly 75% of patients are men, and most patients are >65 years of age at first presentation. Nearly two-thirds of bladder cancers will recur, and approximately 25% will progress to muscle invasive or metastatic disease following conventional cystoscopic surgery.

Bladder Cancer: Incidence by Stage

Stage	Incidence	Cases/year
Superficial Ta, Tis, T1	70%	37,800
Muscle invasive T2, T3a	25%	13,500
Metastatic N+, M+	5%	2,700

Tis = Tumor in situ

The vast majority (approximately 90%) of bladder cancers are transitional cell carcinomas (TCCs), and approximately 70% are superficial (limited to the mucosa and lamina propria) at initial presentation (stage Ta, Tis [Tumor in situ], and T1). Muscle invasive disease (stage T2 and T3a) is diagnosed in approximately 25% of cases, whereas only approximately 5% of patients present with metastatic disease.

Bladder Cancer:
TNM Staging - 1998

Tumor	Stage
[redacted]	
Superficial muscle	T2a
Deep muscle	T2b
Perivesical fat (micro)	T3a
Perivesical fat (macro)	T3b
Px, uterus, vagina	T4a
Pelvic/Abdominal wall	T4b

American Joint Committee on Cancer. *Manual for Staging of Cancer.* 5th ed. Philadelphia, Penn: JB Lippincott Co; 1998.

The American Joint Committee on Cancer TNM (tumor, node, metastasis) staging of bladder cancer as of 1998 is show here.[2] The focus of this presentation will be superficial bladder cancer, including carcinoma in situ (CIS; also known as Tis), noninvasive Ta, and submucosal T1 tumors.

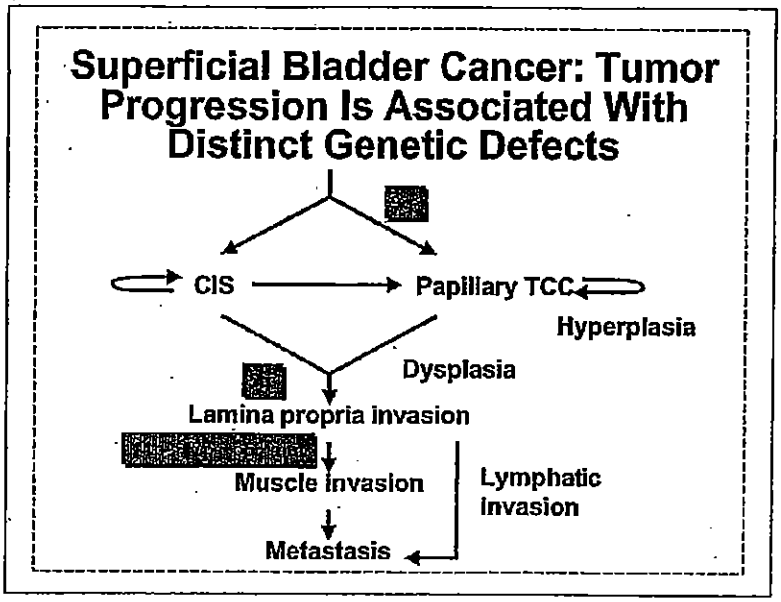
Superficial Bladder Cancer: Rate of Progression and Survival by Tumor Stage and Grade

Stage	Grade	Progression rate to muscle invasion following TUR, %	5-year survival rate, %	10-year survival rate, %
Ta		2 - 5		
	I	0 - 2	100	95
	II	10 - 20	95	89
	III	45 - 50	95	84
T1		20 - 30		
	II	10 - 20	90	78
	III	45 - 50	70	50
Tis		50 - 80	70	55

TUR = Transurethral resection.

Jakse G, et al. *J Urol.* 1987;137:39-43. Stanisic TH, et al. *J Urol.* 1987;138:1158-1161. Utz DC, et al. *Cancer.* 1980;45(suppl 7):1842-1848.

The rate of progression and survival rates vary depending on the stage and histologic grade of the tumor at diagnosis.[3-5] Poorly differentiated high-grade tumors are generally associated with a high rate of muscle-layer invasion and regional or distant metastasis. Low-grad Ta tumors are the least invasive and are associated with excellent 5- and 10-year survival rates. However, up to 50% of grade III Ta and T1 tumors will progress, usually within 2 years of initial therapy, and patients with these tumors have lower survival rates. More than half of patients with CIS will progress to invasive or metastatic disease within 5 years and have a poor long-term prognosis.[6-8] Patients at high risk of progression are candidates for adjuvant intravesical therapy following transurethral resection (TUR) of their primary tumor.



Loss of chromosome 5q is associated with dysplasia and often precedes invasion of the lamina propria. Subsequent loss of chromosomes 11p and 17p, as well as mutations in p53, are associated with muscle and lymphatic invasion, which can lead to systemic metastasis.

Superficial Bladder Cancer: Questions

- Is likelihood of progression predictable at time of initial diagnosis?
- Can metastases be prevented by early intervention?
- What is the best Intervention for patients at high risk of progression?
  - Intravesical therapy?
  - Early cystectomy?
- If random bx's are ⊕, what to do next?

As the previous slides suggest, the risk of progression is somewhat predictable and is correlated with clinical factors such as disease stage, histologic tumor grade, and distinct genetic defects. Likewise, the risk of recurrence has been correlated with high-level expression of vascular endothelial growth factor (VEGF) and nuclear p53 accumulation.[9,10] The most appropriate treatment for patients at high risk of recurrence and progression following TUR remains controversial. It is unclear whether progression and metastasis can be prevented by early aggressive intervention. In patients at high risk of progression, the best intervention may be intravesical therapy or early cystectomy. There is good evidence to suggest that effective intravesical therapy can reduce the rate of recurrence and delay progression, but it is less clear whether intravesical therapy can prevent progression.

AUA

Current issues
- random bladder bx's at time of TURB

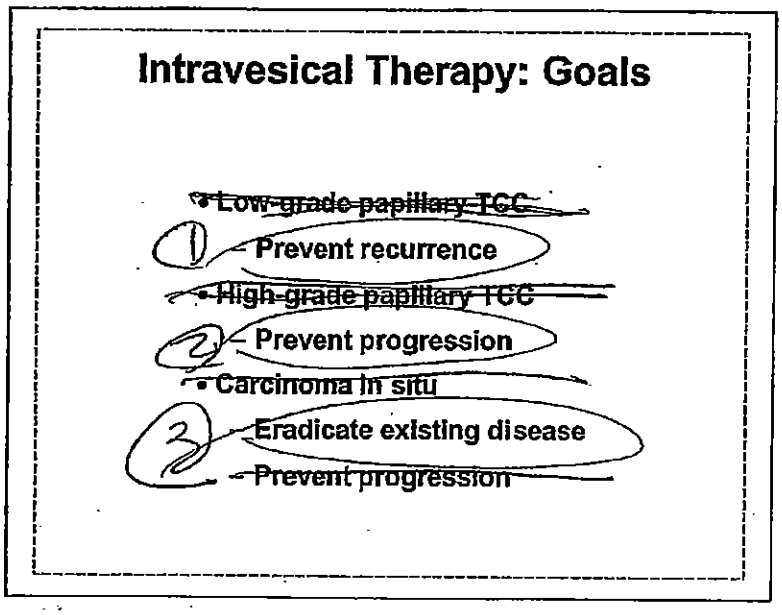
Intravesical Therapy: Indications

(Pts at highest risk & most likely to benefit)

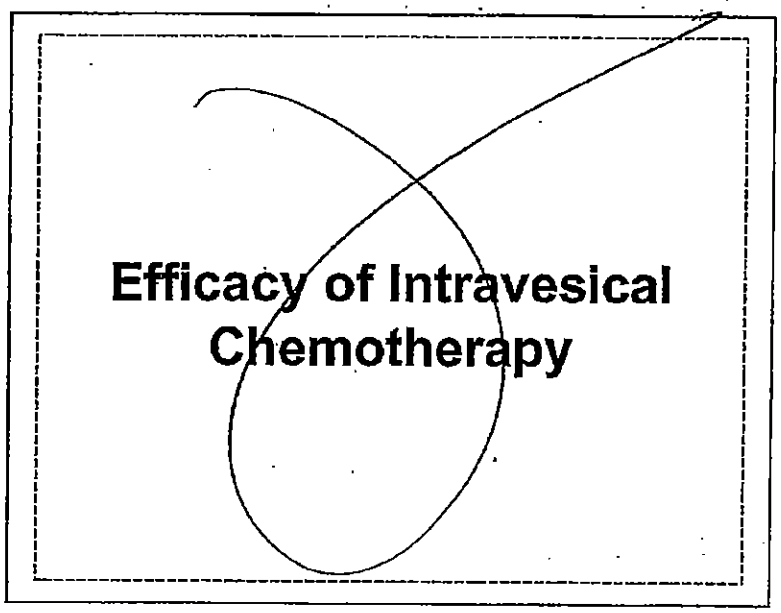
- Multiple tumor recurrences or rapidly recurrent disease
- Lamina propria invasion
- Multifocal disease
- High-grade disease
- Carcinoma in situ ~~or severe dysplasia~~
- Extravesical involvement (prostatic urethra)
- Postresection positive cytology
- Solitary large bladder tumor. (≥ 2 cm).

Superficial bladder cancer patients with multiple tumor recurrences or a recurrence within 3 to 6 months of resection, laminia propria invasion, multifocal or high-grade disease, CIS or severe dysplasia, extravesical involvement, or a positive cytology after TUR are all candidates for intravesical therapy.

add slide – low risk – ~~pTa...~~ generally not be getting intravesical tx



In general, the goals of intravesical therapy are to prevent recurrence and progression while sparing the bladder. In patients with low-grade, papillary tumors, who have a low risk of progression, the primary goal is to prevent recurrence. In patients with high-grade papillary tumors, who have a high risk of progression, the primary goal is to prevent progression. In most patients with CIS and some patients with multifocal papillary disease, residual disease may remain after TUR. Therefore, in those patients, the goal of intravesical therapy is also to eradicate residual disease and prevent progression.



(introduce general tx. options first, before going into tx.),

Current Treatment Options

(Gail) Available treatments
TUR
- Cystectomy – which pts. should have cyst. discussed as 1st line tx.
- immuno
- chemo
- photodynamic tx.

"who would not benefit from cystectomy?"

Next chemo

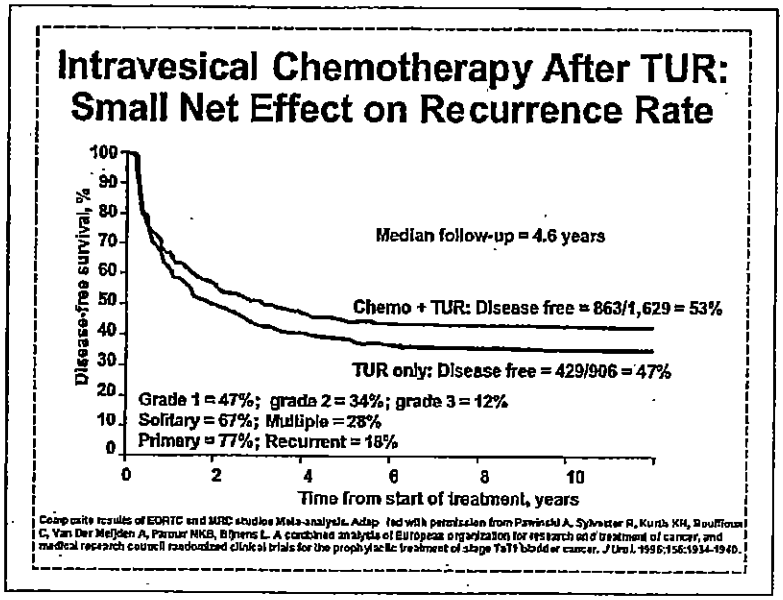
Intravesical Chemotherapy After TUR: Small Net Effect on Recurrence Rate

Agent	Studies	No. of Patients	Recurrence Rate, % Control	Treatment	Net Benefit
Thiotepa	9	1,130	61	49	12
Mitomycin C	6	1,157	53	44	9
Doxorubicin	5	1,389	53	38	15
Overall	22	3,899	54	40	14

Lamm DL, et al. *J Urol.* 1995;153:1444-1450.

Commonly used intravescal chemotherapy agents, including thiotepa, mitomycin C, and doxorubicin, have little net effect on the rate of recurrence in patients with superficial bladder cancer. In a review of 22 prospective, randomized, controlled trials involving nearly 4,000 patients, prophylactic adjuvant chemotherapy reduced the rate of recurrence by only 14% overall.[11] Although 13 trials reported a statistically significant decrease in tumor recurrence with varying durations of follow-up, long-term studies have shown that adjuvant intravesical chemotherapy does not decrease the risk of recurrence compared with TUR alone. Therefore, in light of the substantial toxicity and carcinogenic potential of chemotherapy, intravesical chemotherapy is a poor therapeutic option.

recent data
(Single instillation concept
bargraph from D. Lamm. (Dr. Gomella has slide).
AUA Bladder CA Guidelines — add + try to explain
more up to this section.



Similar results were reported from a meta-analysis of 4 European Organization for the Research and Treatment of Cancer (EORTC) and 2 Medical Research Council (MRC) phase III randomized trials that enrolled patients with primary or recurrent stage Ta or T1 TCC.[12] The majority of patients enrolled in these trials were previously untreated and had solitary primary tumors. Only a small proportion of patients had high-grade disease (12% grade 3), multifocal disease (28%), or recurrent tumors (18%). Thus the risk of recurrence was fairly low. Among 1,629 patients treated with intravesical chemotherapy, 53% remained disease-free at 10-years compared with 47% of 906 patients treated with TUR only. These results support the conclusion that prophylactic adjuvant intravesical chemotherapy produces only a marginal improvement in the rate of recurrence in patients with superficial bladder cancer.

Intravesical Chemotherapy After TUR: No Net Effect on Progression Rate

Agent	Studies	No. of Patients	Progression Rate, %		
			Control	Treatment	Net Benefit
Thiotepa	3	314	6	5	1
Mitomycin C	3	336	7	4	3
Doxorubicin	3	389	13	15	—2
Overall	9	1,039	9	8	1

Adapted with permission from Lamm DL, Riggs DR, Traynelis CL, Nseyo UO. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long-term course of superficial transitional cell carcinoma of the bladder. *J Urol.* 1995;153:1444-1450.

Intravesical chemotherapy has also been shown to have a minimal impact on the risk of progression. Among 10 prospective, randomized, controlled trials that reported progression data, none demonstrated a significant decrease in the rate of progression among patients treated with adjuvant intravesical chemotherapy.[11] Among 1,039 patients treated with thiotepa, mitomycin C, or doxorubicin, there was no net improvement in the rate of progression. Overall, among 2,011 randomized patients, progression occurred in 7.5% of patients treated with intravesical chemotherapy versus 6.9% of patients treated with surgery alone.

Efficacy of Intravesical Immunotherapy